Impact of DEL22q11, trisomy 21, and other genetic syndromes on surgical outcome of conotruncal heart defects

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Objective: Genetic syndromes occur in more than 20% of patients with conotruncal heart defects. We investigated the impact of genetic syndromes on the surgical outcome of conotruncal anomalies in infancy.

Methods: This retrospective study reviews the outcome of 787 patients (median age 6.3 months) who underwent primary (598) or staged (189) repair of a conotruncal defect between 1992 and 2007.

Results: Proven genetic syndrome was diagnosed in 211 patients (26.8%), including del22q11 (91 patients), trisomy 21 (29 patients), VACTERL (18 patients), and other syndromes (73 patients). Primary repair was accomplished in 80.9% of nonsyndromic patients and 74.4% of syndromic patients ($P = .18$) Fifteen-year cumulative survival was 84.3% ± 2.3% in nonsyndromic patients and 73.2% ± 4.2% in syndromic patients ($P < .001$). Primary and staged repair allowed similar 15-year survival (81.4% ± 4.5% vs 79.1% ± 5.1%, $P = .8$). Freedom from noncardiac cause of death was significantly lower in syndromic patients ($P = .0056$). Fifteen-year Kaplan–Meier survival was 87.6% ± 3.9% for del22q11, 95.8% ± 4.1% for trisomy 21, 56.8% ± 6.3% for VACTERL, and 62.3% ± 12.7% for patients with other syndromes ($P = .022$). Total intensive care unit stay was 10.8 ± 4.9 days in syndromic patients and 5.1 ± 1.7 days in nonsyndromic patients ($P < .001$). Freedom from reintervention 15 years after repair was 79.6% ± 4.9% in nonsyndromic patients and 62.4% ± 7.4% in syndromic patients ($P = .007$).

Conclusion: Del22q11 and trisomy 21 do not represent risk factors for mortality after repair of conotruncal anomalies, whereas other syndromes adversely affect the surgical outcome for predominant noncardiac attrition. Higher morbidity and lower mid-term freedom from reintervention can be predicted in syndromic patients.

Supplemental material is available online.

Genetic syndromes occur in more than 20% patients with conotruncal heart defect (CTHD);[1] nevertheless, the impact of this association on the surgical outcome of the cardiac anomalies is still incompletely defined. Previous studies suggested that more than 17% of patients with CTHD carry a 22q11 deletion.[1,2] Moreover, trisomy 21 has been reported in 7% of patients with tetralogy of Fallot (TOF).[3] Patients with TOF with Alagille syndrome carry a mutation in JAG1,[4] and VACTERL, CHARGE, or other syndromes can be associated with TOF[5] and other CTHDs.[6] Patients with CTHD and an associated genetic syndrome present a challenge to the cardiac surgeon and may face additional risk for primary repair. This study was designed to document the impact of genetic defects on the current surgical outcome of CTHD.

MATERIALS AND METHODS

We reviewed the surgical and medical records of all patients who underwent repair of a CTHD at Bambino Gesù Hospital, Rome, Italy, between January 1992 and January 2007. Informed parental consent and institutional review board approval were obtained for this retrospective study. On the basis of the recommendations of Goldmuntz and colleagues,[1] 6 CTHDs were included in this study because of their possible association with genetic defects, specifically TOF, TOF pulmonary atresia (PA), TOF PA major aortopulmonary collaterals (MAPCAs), truncus arteriosus (TA), double-outlet right ventricle (DORV), and interrupted aortic arch (IAA). Posterior malalignment-type ventricular septal defect (VSD) was not included because it was always found to be associated with IAA in this cohort. Patients with DORV and straddling atrioventricular (AV) valve, hypoplastic AV valve, unbalanced ventricles, or heterotaxy syndromes were excluded because of the rare option of a 2-ventricle repair in these malformation syndromes. Patients with trisomy 13 and 18 also were excluded to avoid the bias of the short and unfavorable natural history in these syndromes. Patients who transferred their care to our unit, but were previously treated at other centers, were excluded from this study. After informed parental consent, a genetic consult by a clinical geneticist (M.C.D.) was obtained to rule out the presence of a genetic syndrome, searching for dysmorphic features, growth anomalies, mental retardation (>6 months of age), and associated malformations. A blood sample was drawn for prospective chromosomal analysis of peripheral lymphocytes using standard and high-resolution techniques. Until 1994, search for microdeletion 22q11.2 relied on Southern hybridization with HD7k probe detecting hemizygosity for the D22S134

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Received for publication Sept 9, 2008; revisions received Feb 16, 2009; accepted for publication March 11, 2009; available ahead of print May 25, 2009.

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J Thorac Cardiovasc Surg 2009;138:565-70
0022-5223/$36.00

doi:10.1016/j.jtcvs.2009.03.009

Abbreviations and Acronyms

CTHD = conotruncal heart defect
DORV = double-outlet right ventricle
IAA = interrupted aortic arch
MAPCAS = major aortopulmonary collaterals
PA = pulmonary atresia
RV = right ventricle
RVOT = right ventricular outflow tract
TA = truncus arteriosus
TOF = tetralogy of Fallot
VSD = ventricular septal defect

region. After 1994, detection of deletions of chromosomal region 22q11 relied on fluorescent in situ hybridization using the Sc11.1 and N25 probe. Screening was universal for del22q11 and selective for other genetic abnormalities (JAG1, NKX2.5, and others). Fluorescent in situ hybridization analysis with the ENL probe was performed in subjects with clinical characteristics of Williams syndrome. Analysis of medical records with clinical descriptions of associated anomalies, prenatal and postnatal instrumental investigations, and autoptic findings were obtained for the patients who did not undergo genetic testing at birth. Preoperative 2-dimensional and Doppler echocardiography were performed in all patients. Preoperative cardiac catheterization was performed in 187 patients when pulmonary arborization abnormalities such as discontinuous or hypoplastic pulmonary artery branches, multiple aortopulmonary collaterals, presence of multiple VSDs, or anomalous coronary artery patterns were suspected at echocardiography. Cardiac catheterization allowed calculation of total neopulmonary arterial index, pulmonary arterial index, and pulmonary artery-to-collateral arteries lung segment perfusion ratio in the preoperative evaluation of unifocalization and repair of TOF-PA-MAPCAs.[7]

Operative Technique

Complete repair was accomplished under hypothermic cardiopulmonary bypass (25°C–28°C) for most CTHDs, whereas aortic arch reconstruction in IAA was achieved under deep hypothermic (18°C) circulatory arrest. A systemic-to-pulmonary shunt, if present, was divided. Ventricular septation was accomplished through a transventricular approach in TA, TOF-PA-MAPCAs, and occasionally in DORV, whereas a transatrial approach was preferred in TOF and IAA. VSD closure with 1-stage unifocalization in TOF-PA-MAPCAs was guided by an intraoperative pulmonary flow study. Relief of right ventricular outflow tract (RVOT) obstruction in TOF and DORV was achieved through a combined transatrial-transpulmonary approach. RVOT reconstruction was accomplished after calibration of the pulmonary annulus and PA branches. Preservation of the pulmonary annulus by complete transatrial repair or limited infundibular patch plasty was accomplished when the Z-score for pulmonary annulus diameter was at least –2. Transannular patching was used when the pulmonary annulus Z-score was less than –2. Conduit interposition between the right ventricle (RV) and the pulmonary confluence was used when indicated (PA, truncus). Associated anomalies were corrected simultaneously. RV pressure and PA saturation were measured after discontinuation of cardiopulmonary bypass to detect residual outflow obstruction and left-to-right shunting. Intraoperative transesophageal echocardiography was performed when residual lesions were suspected after repair.

Follow-up

All surviving patients were followed in the pediatric cardiology outpatient clinic. Clinical examination, 12-lead electrocardiogram, and 2-dimensional echocardiography were performed at regular intervals to estimate tricuspid valve and RV function/pressure and to detect residual lesions, pulmonary artery branch stenosis, or residual aortic arch stenosis. Hemodynamically significant residual lesions were confirmed at cardiac catheterization before surgical or interventional procedures. Closing time for follow-up was June 2007. Mean follow-up was 62.1 ± 23 months (range 6–178 months) and was complete and updated in 765 patients (97.2%).

Statistical Analysis

Statistical analysis was conducted with the SAS Statview 1998 statistical software (SAS Institute Inc, Cary, NC). Chi-square analysis was used to compare discrete variables between syndromic and nonsyndromic patients, and continuous variables (expressed as mean ± standard deviation) were compared by unpaired *t* testing. Categoric analysis was conducted by chi-square and Fisher's exact tests. Freedom from time-related events was conducted according to actuarial or Kaplan–Meier technique; the resulting curves with 95% confidence limits were compared with log-rank testing, and nomograms of the hazard function were obtained . Selected and separate end points were defined as death, reoperation, or interventional procedure. Early mortality was defined as death within 30 days from surgery or before hospital discharge. Variables associated with an increased risk of death and reoperation were assessed by univariate logistic regression, multiple logistic regression, and Cox proportional risk multivariate analysis. To avoid colinearity among covariates, only mutually exclusive variables were entered in the multivariate analysis. Therefore, all genetic syndromes were compacted under the covariate ''genetic syndrome.''

RESULTS

Between January 1992 and January 2007, 787 consecutive patients (438 male and 349 female) underwent primary (598) or staged (189) repair for CTHD. Median age at repair was 6.3 months (range 0.1–214 months)

Anatomy

Surgical anatomy included 540 patients with TOF (68.6%), 58 patients with TOF-PA (7.4%), 63 patients with TOF-PA-MAPCAs (8%), 45 patients with TA (5.7%), 45 patients with DORV (5.7%), and 36 patients with IAA (4.6%). Type A IAA was diagnosed in 9 patients, type B IAA was diagnosed in 26 patients, and type C IAA was diagnosed in 1 patient.

Genetic Syndromes

A clinical genetic evaluation was obtained in 755 of 787 patients (95.9%), including 667 of 697 survivors (95.6%) and 88 of 90 nonsurvivors (97.7%). Enrollment was refused in 7 patients. Blood was drawn for chromosomal analysis of peripheral lymphocytes using standard and high-resolution techniques in 733 of 787 patients (93.1%). Proven genetic defect was diagnosed in 211 patients (26.8%), including del22q11 (91 patients), trisomy 21 (29 patients), VACTERL (18 patients), and other syndromes (73 patients). Approximately one third of syndromic patients with CTHDs carried a rare genetic defect and were unsuitable for syndrome-specific analysis. This heterogeneous group of patients was therefore arbitrarily defined as ''other syndromes'' to allow for meaningful statistical analysis and included CHARGE (15 patients), Noonan (11 patients), Cantrell's (6 patients), Kabuki (5 patients), Klippel Feil (4 patients), Turner (2